REMARKS

Applicants request entry of the amendment, in which claim 1 is cancelled, claims 2, 6, and 11 are amended, and new claims 15-28 are added. The amendments are fully supported by the specification and introduce no new matter.

With the entry of the foregoing amendments, claims 2-28 are pending in the application. The Examiner has maintained the restriction requirement and only elected Group I claims 1-12 were examined; claims 13 and 14 have been withdrawn from consideration. Claim 11 is objected to because of informalities; claims 1 and 6-12 stand rejected under 35 U.S.C. 112, second paragraph; claims 4 and 5 stand rejected under 35 U.S.C. 112, first paragraph; claims 1, 11, and 12 stand rejected under 35 U.S.C. 102(b); and claims 1-12 stand rejected under 35 U.S.C. 103(a).

In view of the amendments above and the arguments below, the Applicants respectfully request reconsideration on the merits of this application.

Objections to the claims

Claim 11 is objected to for informalities; specifically, an "of" was omitted between "step" and "culturing", and an "a" was omitted between "having" and "bacteriorhodopsin". Applicants have corrected these typographical errors by amending the claim 11.

Rejections under 35 U.S.C. 112, second paragraph

Claims 1 and 6-12 stand rejected as being indefinite for the recitation of "a structurally analogous sequence" because the Examiner asserts that the definition provided in the specification (page 10, lines 2-7) does not allow one skilled in the art to determine what is or is not encompassed by the claims. Because the art is equivocal as to the precise relationship between bacteriorhodopsin and G-protein coupled receptors (GPCRs), one skilled in the art could not rely on the art to identify unambiguously analogous structures between bacteriorhodopsin and GPCRs.

Applicants have cancelled claim 1 without prejudice, and rewritten claim 2 as an independent claim. Claim 6 has been amended to include a limitation to a polynucleotide encoding the protein of claim 2, which is not indefinite. Claims 7-10 are drawn to a genetic construct comprising the sequence of claim 6, or to an archaebacterium comprising a genetic construct comprising the sequence of claim 6. Claims 11 has been amended to recite culturing an archaebacterium "according to claim 8"; claim 12, which depends from claim 11, includes all of

the limitations of claim 11. Applicants respectfully request that the rejection of claims 6-12 under 35 U.S.C. 112, second paragraph be withdrawn.

Rejections under 37 C.F.R. 112, first paragraph

Claims 4 and 5 stand rejected under 35 U.S.C. 112, first paragraph for lack of enablement. The Examiner acknowledges that the specification is enabling for chimeric bacteriorhodopsin GPCR chimeras capable of activating GTP-GDP exchange on a G-protein *in vitro*, wherein the GPCR is an opsin, such as bovine rhodopsin, but asserts that the specification does not enable claims 4 and 5, wherein the GPCR could be any GPCR. The Examiner does not assert that the Applicants have provided insufficient guidance to allow one of ordinary skill in the art to make chimeric proteins in which a portion of the intracellular loop three region of bacteriorhodopsin is replaced with a portion the intracellular loop 3 region from a G protein coupled receptor. Rather, the Examiner has raised the question of whether Applicants have enabled chimeric proteins that are able to affect the rate of GTP-GDP exchange on a G protein.

Applicants respectfully submit that the specification provides sufficient guidance to permit one skilled in the art to make and use a chimeric protein according to claims 4 or 5 without undue or unreasonable experimentation. The only Examples provided in the specification concerning the interaction between a chimeric GPCR protein and the corresponding G protein relate to GTP-GDP exchange using bacteriorhodopsin-rhodopsin chimeric protein and transducin. However, claim 2, from which claims 4 and 5 depend, was found to be fully enabled by the specification. Additionally, Applicants disclose a GTP-GDP exchange assay for assessing the rate of GTP-GDP exchange on the corresponding G protein.

Applicants respectfully submit that the claims are fully enabled because, using the Applicants' disclosure, one of ordinary skill in the art could readily make chimeric GPCR proteins according to the claimed invention and evaluate the proteins for the ability to interact with the corresponding G protein using a GTP-GDP exchange assay. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Commission, 1983). Factors to be considered in determining there is sufficient evidence to support a determination that a disclosure does not meet the enablement requirement and whether any necessary experimentation is "undue" include:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the prior art;

(4) The level of one of ordinary skill;

(5) The level of predictability in the art;

(6) The amount of direction provided by the inventor;

(7) The existence of working examples;

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404; MPEP 2164.01(a).

In conducting an analysis under Wands, one must consider the level of skill in the art, which, in the discipline of molecular biology, is very high. It would be a matter of routine experimentation for one of ordinary skill in the art to make the chimeric proteins of the present invention and to test the proteins for the ability to affect the rate of GTP-GDP exchange on a G protein. Another factor to be considered is the guidance provided by the specification. The specification sets forth guidance concerning constructing the chimeric proteins, and discloses a GTP-GDP exchange assay for determining whether a chimeric protein affects the rate of GTP-GDP exchange. Although the creation of chimeric proteins and screening for the ability to affect the rate of GTP-GDP exchange requires some time and effort, it does not constitute "undue" experimentation because such work is fairly routine to one skilled in the art.

Applicants have also provided working examples of bacteriorhodopsin-rhodopsin chimeric proteins that promote GTP-GDP exchange on transducin. Applicants' disclosure is the first report of a bacteriorhodopsin G-protein coupled receptor chimera with the ability to promote GTP-GDP exchange on a G protein. Although it may be that not every chimeric protein according to claim 2 will have the ability to promote GTP-GDP exchange, Applicants need not demonstrate that every chimeric protein according to claim 2 will have the ability to affect GTP-GDP exchange in order to satisfy the enablement requirement.

Applicants respectfully request that the rejection of claims 4 and 5 under 35 U.S.C. 112, first paragraph be withdrawn.

Rejections under 35 U.S.C. 102(b)

Claims 1, 11, and 12 stand rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,641,650 (the '650 patent). The '650 patent is characterized as disclosing a bacteriorhodopsin protein amino acid sequence (the signal sequence or C-terminal sequence) in

which the remaining part of the bacteriorhodopsin (i.e., "at least a portion") was replaced with the structurally analogous region of a G-protein receptor protein. The '650 patent is also cited as teaching a method of producing a chimeric protein according to claims 11 and 12.

Applicants have cancelled claim 1, rendering moot this rejection. Claims 11 and 12 have been amended to clarify that the method employs an archaebacterium of claim 8, which is novel. Therefore, Applicants respectfully request that the rejections under 35 U.S.C. 102(b) be withdrawn.

E. Rejections under 35 U.S.C. 103(a)

Claims 1-3 and 6-12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Popot *et al.*(Current Opinion in Biotechnology 6:394-402, 1995) in view of Hoflack *et al.* (Trends in Pharm. Sci. 15:7-9, 1994). Claims 4 and 5 stand rejected over Popot *et al.* and Hoflack *et al.* in view of Shi *et al.*(J. Biol. Chem. 270:2212-2119, 1995). Applicants note that the Examiner indicated in the Office Action and on the Notice of References Cited that Popot *et al.* publication was published in 1999. However, the year given on the front page of the article appears to be 1995. If, in fact, the Popot *et al.* publication became available after Applicants' priority date of September 3, 1998, it does not meet the requirements of a reference and the rejection should be withdrawn. However, for purposes of this response, Applicants will assume that Popot *et al.* is available as a reference.

Popot *et al.* is cited as teaching "chimeric constructs of bacteriorhodopsin and G-protein receptors can be made for the purposes of functional and structural investigations (p. 396, column 1); that bacteriorhodopsin can be used as a 'benchtop' to arrange engineered loops (p. 397, col. 2); and that a "wealth of data indicates that most of the six loops connecting the transmembrane helices in bacteriorhodopsin can be *tampered with* to large extents and at least three of them can be *cut* without preventing refolding of the proteins (e.g. cytoplasmic loop III, ref. 61)" (emphasis added). Hoflack *et al.*is characterized as teaching that it is "old and well established that bacteriorhodopsin is famous as a template to construct three dimensional models of G-protein coupled receptors". Popot *et al.* is said to provide the motivation to construct chimeric bacteriorhodopsin GPCRs because it teaches that bacteriorhodopsin can be used as a 'benchtop' on which to arrange engineered loops designed to form binding or catalytic sites. The Examiner concludes that it would have been obvious to construct chimeric bacteriorhodopsin/GPCRs according to claims 1-3 and 6-12, and that the construction of a particular chimera in which amino acid residues 171-179 of bacteriorhodopsin were replaced is a matter of routine

optimization.

Applicants respectfully disagree with the Examiner's characterization of the prior art. Popot *et al.* teaches that experiments showing assembly of functional molecules from fragments of dissected α-helical membrane proteins (p. 395, column 2) opens the possibility to reconstitute proteins from fragments for the purpose of functional or structural investigations, which obviates the need to engineer a new construct for each combination to be tested (p. 396, col. 2).

At page 397, column 2, Popot *et al.* does state that "most of the six loops connecting the transmembrane helices in bacteriorhodopsin can be *tampered* with to large extents, and at least three of them can be cut without preventing refolding of the protein (see [61] and references therein)." However, contrary to the Examiner's assertion, neither Popot *et al.* nor the title of reference 61 cited therein specifically refer to cytoplasmic loop III, nor do they teach or suggest replacing a portion of bacteriorhodopsin cytoplasmic loop III with a portion of cytoplasmic loop III from a G protein coupled receptor. Popot *et al.* further teaches that two unspecified cytosolic loops of rhodopsin can be cut without preventing correct folding. Applicants note that the Popot *et al.* publication is a review article, and contains very general, imprecise statement; Reference 61 is not of record in the instant application.

Hoflack *et al.* does not cure the deficiencies of Popot *et al.* Hoflack *et al.* explores the question of whether bacteriorhodopsin is a valid model for studying the three dimensional structures of G protein-coupled receptors, given reported differences in electron diffraction maps of bovine rhodopsin and bacteriorhodopsin. Although Hoflack *et al.* states that it is "old and well established that bacteriorhodopsin is famous as a template to construct three dimensional models of G-protein coupled receptors," it does not teach replacing a portion of the intracellular loop 3 domain with a portion of the intracellular loop 3 region from a G protein-coupled receptor, let alone replacing amino acid residues 171-178 of the intracellular loop 3 domain with a portion of the intracellular loop 3 region from a G protein-coupled receptor.

A prima facie case of obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) the art reference or combination of references must teach all of the claim limitations (MPEP 2142). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (MPEP 2143).

Claim 1 has been cancelled without prejudice, rendering moot this rejection. With respect

to claims 2, 3, and 6-12, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness for the reasons set forth below.

Popot *et al.* and Hoflack *et al.* do not combine to teach or suggest all of the claim limitations. Construction of a chimera in which the intracellular loop 3 domain region of bacteriorhodopsin is replaced with a portion of the intracellular loop 3 domain of a G protein coupled receptor protein is not disclosed in the art of record. Furthermore, replacement of amino acid residues 171-179 of the intracellular loop 3 domain region of bacteriorhodopsin with a portion of the loop 3 domain of a GPCR protein is not a matter of routine optimization of operating parameters.

Applicants respectfully submit that a chimeric bacteriorhodopsin G protein-coupled receptor protein in which the bacteriorhodopsin amino acid sequence specifically recited in claim 3 is replaced with amino acid residues from the intracellular loop III of a G protein-coupled receptor is not simply a matter of routine optimization of operating parameters. It is not reasonable to characterize the selection and substitution of amino acid residues 171-179 of bacteriorhodopsin with the loop three region from another protein as "routine optimization of operating parameters". The difference between the claimed invention and the prior art is considerably greater than the type of difference that should be considered "routine optimization" (MPEP 2133.05(b). Applicants respectfully submit that the differences between art cited by the Examiner and claim 3 are substantial, and not a matter of routine optimization.

Claims 4 and 5 stand rejected over Popot *et al.* and Hoflack *et al.* in view of Shi *et al.*Popot *et al.* and Hoflack *et al.* are cited for the reasons set forth above. The Examiner characterized Shi *et al.* as disclosing that cytoplasmic loop III is critical to G-protein activation. He concluded that it would be obvious to produce a bacteriorhodopsin-bovine rhodopsin chimera wherein the third cytoplasmic loop of bacteriorhodopsin is substituted for that of a G protein coupled receptor.

Shi *et al.* teaches that bovine rhodopsin mutants in which alanine residues in the various regions were mutated have reduced ability to catalyze GTP-GDP exchange. Applicants acknowledge that Shi *et al* .indicates that the cytoplasmic loop III region of bovine rhodopsin is important to GTP-GDP exchange (p. 2218, first full paragraph). However, Shi *et al.* does not teach that the loop III region of bovine rhodopsin is alone sufficient to catalyze GTP-GDP exchange. In fact, Shi *et al.* teaches away from the claimed invention in that Shi *et al.* discloses data "that suggest for the first time that domains that participate in the activation of rhodopsin kinase reside in loops I and II", and that a highly conserved arginine residue (Arg^{135}) between the

third transmembrane domain and Loop II appears to be critical for binding and activation of transducin (p. 2118, first column, lines 1-13). Shi *et al.* does not cure the deficiencies of Popot and Hoflack in that it does not teach or suggest replacing amino acid residues in the loop III region of bacteriorhodopsin with the loop III of a G protein-coupled receptor to create a bacteriorhodopsin G protein-coupled receptor having the ability to catalyze GTP-GDP exchange on the G protein corresponding to the G protein-coupled receptor.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. 103(a) be withdrawn.

As the application is now in condition for allowance, Applicants request reconsideration of the claims on the merits of the application, withdrawal of the outstanding rejections, and allowance of the claims.

Check number 43437 in the amount of $108.00 is enclosed to cover the fee for the additional claims added by amendment. No other fee is believed owing in connection with this submission. If a fee is owed, please charge such fee to Deposit Account No. 50-0842.

Should Examiner Brannock feel that any other point requires consideration or that the form of the claims can be improved, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: January 22, 2002

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MARKED UP CLAIMS SHOWING AMENDMENTS

CLAIMS

2. A chimeric fusion protein comprising a bacteriorhodopsin [The] protein amino acid sequence [of claim 1], wherein the protein comprises substantially all of the amino acid sequence of bacteriorhodopsin except the intracellular loop 3 domain, wherein the intracellular loop 3 domain of bacteriorhodopsin is replaced by at least a portion of the intracellular loop 3 domain of a G protein-coupled receptor protein.

6. A polynucleotide sequence encoding the chimeric fusion protein of claim [1] 2.

11. A method of producing a bacteriorhodopsin/G protein-coupled receptor chimeric fusion protein comprising the step of culturing [an] the archaebacterium of claim 8 [comprising a genetic construct having a polynucleotide sequence that encodes a chimeric fusion protein having bacteriorhodopsin protein amino acid sequence in which at least a portion of the protein is replaced with the structurally analogous region of a G protein-coupled receptor protein, the polynucleotide sequence operably connected to a promoter sequence functional in the archaebacterium, wherein the polynucleotide sequence of the construct is expressible in the archaebacterium,] under suitable conditions and for a period of time sufficient to allow expression of the chimeric fusion protein.